Appln No.: 10/075,947
Amendment Dated: February 4, 2005
Reply to Office Action of October 4, 2004

REMARKS/ARGUMENTS

This is response to the Official Action mailed October 4, 2004. Reconsideration of the Application, as amended, in view of the remarks herein is respectfully requested.

Applicants enclose a request for an extension of time and enclose the appropriate fee. Should additional extensions be required for this paper to be timely, they are hereby requested. The Commissioner is authorized to charge any additional fees or credit any overpayment to Deposit Account No. 15-0610.

The specification has been amended to reflect the status of the parent case, and an amendment to the title has been made in accordance with the Examiner's remarks.

Claim 41 has been amended to correct the error in dependency. This amendment should overcome the rejection under 35 USC § 112.

In the present case, the claims relate to T cells expressing a recombinant single chain anti-G_{D2} antibody. The Examiner has indicated that claims directed to specific sequences are allowable, but has rejected the broader generic claims under 35 USC § 103 as obvious over a combination of references. Applicants respectfully traverse this rejection.

The Examiner states that Eshhar teaches T cells that express a single chain antibody, but acknowledges that Eshhar does not teach antibodies that target the GD2 antigen. To overcome this deficiency the Examiner cites Bernhard which teaches a bispecific anti-GD2 - anti-CD3 antibody that binds to T cells via the anti-CD3 end and tumor cells via the anti-GD2 end to result in tumor lysis. Based on these two teachings, the Examiner says that expressing a single chain anti-GD2 antibody in T cells would have been obvious.

Effectively, the Examiner's argument is that now that Eshhar has made his teaching, every class of T cells expressing a particular antigen becomes obvious as soon as someone identifies the antigen as a worthy target. The fact that the Examiner has picked out Bernhard from the myriad papers describing tumor antigens is not based on any teaching in the references, but rather is guided solely by the scope of the present invention. This circumstance is indicative of a rejection that is at best based on an improper "obvious-to-try" type of standard.

As the courts have observed, "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 140, 231 USPQ 644, 647 (Fed. Cir. 1986) (citing *ACS Hosp. Syss., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). "[T]he factual inquiry whether to

combine references must be thorough and searching." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001).

The most that Bernhard offers is the identification of GD2 as a marker with therapeutic **potential.** The composition used is a bispecific antibody, that is fabricated from an antibody fragment known to bind to the target GD2 and another antibody known to bind to CD3. This process is done *in vitro.* Both portions of the antibody are free in solution. In contrast, in the Eshhar references, the scFv is expressed in situ by the cells. This difference between the references in both philosophy and methodology is substantial, and as a result the references are not combinable to establish a *prima facie* case of obviousness.

Moreover, it is important to bear in mind that the pending claims are directed to compositions (T cells) and not to methods. 35 USC § 103 expressly states that patentability is to be considered independent of how an invention was made. Thus, it is simply not relevant that the tools or techniques employed to arrive at the invention were known. Further, as the CCPA observed in *In re Kratz*, 201 USPQ 71, 76 (CCPA 1979) it is improper try to substitute skill in the art for statutory prior art.

The *Kratz* case presents an apt parallel to the present claims. In that case, the invention was a composition that tasted like strawberries. Because the compound was isolated by the "obvious" method of chopping up and analyzing strawberries, the composition was deemed obvious. In reversing this rejection, the CCPA observed that even if all of the component molecules in strawberries had been set forth in a list in the prior art, that list did not "direct[] one having ordinary skill in the art to any particular compound for any purpose." 201 USPQ at 76. Thus, the compound claimed was not obvious.

In the present case, the knowledge of the technique of Eshhar and myriad possible targets is at best a list of things to be experimented on. The tools may exist based on Esshar (although this is not admitted), but that is not the question which must be posed. Rather, the question to be posed is whether the T cells that are the subject of Applicants claims, would have been obvious based on teachings in the art. Applicants submit this is not the case, since the techniques of Bernhard are entirely different from those of Eshhar.

Reliance by an Examiner on the availability of the tools by which an invention was made, as opposed to actual suggestions in the art pointing to the claimed subject matter, has been criticized in *In re Bell*, 26 USPQ 2d. 1529 (Fed. Cir. 1993) and *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995). The *Deuel* court stated:

> We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the

> question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.

34 USPQ2d at 1215. *In Deuel*, the prior art taught cloning techniques, and the partial amino acid sequence for which a nucleic acid sequence was claimed. The techniques for finding out the nucleic acid sequence were admittedly well known. The result, however, that is the specific nucleic acid sequence, was not known, and did not become obvious simply because it was discoverable using known and potentially routine techniques.

In the present case, the methods taught in Eshhar and the method of Bernhard are not interchangeable. Bernhard observes that use of bi-specific antibodies can "bypass the normal specificity of the T-cell antigen receptor [and] can theoretically activate all of a cancer patient's cytotoxic T lymphocytes to kill cancer cells." (Page 469, Col. 2). This result is not achieved using Eshhar's methods. Further, the Examiner's position that obtaining the amino acid sequence from Bernhard MAb, and then get the cDNA sequence from this so as to produce the single chain antibody in a T cell is contrary to the holding in *Duell* not once, but twice, since two new compositions must be determined. In addition, the proposed combination results in a potential reduction in activity as compared to Bernhard, as well as doubt as to whether GD2 would even be presented properly to produce a result in the Eshhar method. The T cells therefore are not obvious, and the rejection should be withdrawn.

The other two references, Hansen and Epenetos. do not alter this conclusion with respect to the independent claim because they are not relevant to the basic issue. Nevertheless, it is noted that here to the Examiner's position is flawed. These references are cited to show antibody- enzyme or antibody-streptavidin conjugates. In each case, however, the material used in the reference is an extracellular prepartion of the expressed protein. There is no teaching in these references that shows or suggests making T cells expressing these materials. Thus, the rejection of these claims are further flawed.

For the foregoing reasons, Applicants submit that all pending claims are in form for allowance. Favorable reconsideration is respectfully urged.

Respectfully submitted,

Marina T. Larson Ph.D.
PTO Reg. No. 32,038
Attorney for Applicant
(970) 468-6600